REMARKS

Applicants thank the Examiner for her review of the instant application. Applicants' priority claim has been amended, and Claim 4 has been amended to better define Applicants' claimed invention. No new matter has been added by these amendments. Claims 1-5 remain pending and are presented for further examination. For the reasons stated below, Applicants respectfully traverse the rejection of the pending claims.

Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of Claims 1-5 under 35 U.S.C. § 101 as lacking a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Actions. The PTO asserts that one skilled in the art would not know how to use the claimed invention. According to the PTO, "the present Specification fails to disclose the physiological significance of the PRO1270 antibody or what the correlation between PRO1270 mRNA and PRO1270 polypeptide expression is, or the significance of any such correlation in lung tumors." *Office Action* at 3. The PTO continues to rely on the previously cited references, stating that "[w]hen viewed with the evidence of record as a whole, there is no correlation between gene underexpression, mRNA levels and protein levels." *Office Action* at 11.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the Examiner has not met the PTO's burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However, even if the Examiner has met the PTO's initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants remind the PTO that the asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1270 polypeptide is expressed at least two-fold higher in normal lung tissue compared to lung tumor tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a corresponding change in the level of the encoded protein, e.g. a decrease;

3. Given Applicants' evidence that the mRNA for the PRO1270 polypeptide is differentially expressed in lung tumor tissue compared to normal lung tissue, it is more likely than not that the PRO1270 polypeptide is likewise differentially expressed in these tumors; the PRO1270 polypeptide is therefore useful as a diagnostic tool to distinguish lung tumor tissue from normal lung tissue.

Applicant's maintain that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

The PTO has Concluded that the data in Example 18 are Sufficient to Establish the Utility of the Claimed Invention

As an initial matter, Applicants point out that in other applications filed by Applicants that rely *on data from the exact same disclosure, Example 18*, and in which Applicants have submitted *substantially the same references* in support of their asserted utility, the PTO has concluded that: "[b]ased on the totality of evidence of record, **one of skill in the art would find it more likely than not that an increase in message as measured by RTPCR would be predictive of an increase in protein expression levels,** absent evidence to the contrary. Therefore, the data presented in Example 18, which demonstrates differential expression of nucleic acids encoding PRO1180, also supports a conclusion of differential expression of PRO1180 polypeptide. Therefore, one of ordinary skill in the art would be able to use the PRO1180 polypeptide diagnostically for distinguishing normal kidney and rectal tumor tissues compared to kidney tumor and normal rectal tissue, as asserted by Applicant." See *Examiners Reasons for Allowance* in pending Application No. 10/063,529. See also *Examiners Reasons for*

Allowance in Application No. 10/063,530, No. 10/063,524, No. 10/063,582, and No. 10/063,583, all of which conclude that the data presented in Example 18, which demonstrate differential expression of the nucleic acids encoding certain PRO polypeptides, also support a conclusion of differential expression of the PRO polypeptides, making the claimed PRO polypeptides and antibodies that bind the PRO polypeptides useful for diagnostic purposes.

Applicants therefore request that the Examiner recognize the utility of the claimed invention, supported by the data presented in Example 18 and Applicants numerous cited references, as was done in the other applications referenced above.

The Previously Cited References Provide Evidence that Changes in mRNA Levels are Correlated with Changes in Protein Levels

Applicants incorporate by reference their previously submitted arguments in regard to Hu *et al.* and will not reiterate those arguments here. However, Applicants will once again explain why the PTO's reliance on Hu is misplaced. Hu bases his conclusions on data generated from high throughput microarrays:

> In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study. *Hu* at 405, left column, first paragraph (emphasis added).

As Applicants previously pointed out, Applicants are relying on a more accurate and reliable method of assessing changes in mRNA level, namely quantitative PCR analysis. Applicants submit herewith as Exhibit 1 a reference by Kuo *et al.*, (Proteomics 5(4):894-906 (2005)), in which the authors state that PCR is a "more reliable and sensitive" than microarray technology. *Kuo et al.* at Abstract (emphasis added). Thus, even if accurate, Hu's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

Applicants submit that Kuo supports their assertion that Applicants' PCR data are more accurate and reliable than the microarray data relied on by Hu. Because PCR is more accurate and reliable than microarrays, conclusions regarding the relevance of mRNA transcript changes based on microarray data, such as those set forth in Hu, are not applicable to data generated using the more reliable method. Kuo supports this assertion because it is evidence that one of skill in the art would regard PCR as a more accurate and reliable method of assessing changes in mRNA.

In support of its arguments, the PTO newly cites references by King et al. and Lee et al. which discuss microarray gene expression studies. Applicants submit that the PTO has misunderstood the data upon which Applicants rely. The PTO states: "all of Applicants' newly cited references measure mRNA with assays other than microarray, which is the assay utilized in Example 18 of the specification." *Office Action* at 14. Applicants once again point out that Example 18 of the specification clearly states that oligonucleotide probes constructed from the PRO polypeptide encoding nucleotide sequences "were employed in standard **quantitative PCR amplification reactions** with cDNA libraries isolated from different human tumor and normal human tissue samples and analyzed by agarose gel electrophoresis so as to obtain a quantitative determination of the level of expression of the PRO-polypeptide encoding nucleic acid in the various tumor and normal tissues tested." Thus, Example 18 of the specification does not utilize microarray technology, but rather, uses PCR analysis, a more accurate and reliable method of assessing changes in mRNA level.

Applicants also note that the PTO again seems to have misinterpreted the data presented in the present application when it states "although the 'universal control' of the instant application is derived from tissues of epithelial origin (p. 135, line 1 of the instant specification), there is no teaching in the specification that any epithelial samples were derived from lung... It is not clear as to why the tumor tissues in Example 18 are not compared to single organ control samples." *Office Action* at 7.

As an initial matter, Applicants point out that page 135, line 1 of the instant specification reads as follows: "This invention is particularly useful for screening compounds using PRO polypeptides..."

Next, Applicants point out that Example 18 of the specification clearly states that oligonucleotide probes constructed from the PRO polypeptide encoding nucleotide sequences "were employed in standard quantitative PCR amplification reactions with cDNA libraries isolated from **different human tumor and normal human tissue samples** and analyzed by agarose gel electrophoresis so as to obtain a quantitative determination of the level of expression of the PRO-polypeptide encoding nucleic acid in the various tumor and normal tissues tested." Thus, the tumor tissues listed in Example 18 were in fact compared to single organ control samples – the results listed in Example 18 report the tissues where differential expression was

detected. In this case, Example 18 shows that the PRO1270 mRNA was differentially expressed in lung tumors versus normal lung tissue. Thus, the PTO has no basis for questioning Applicants data as set forth in Example 18.

Applicants now turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1270 polypeptide in lung tumors, it is likely that the PRO1270 polypeptide is likewise differentially expressed in these tumors; and proteins differentially expressed in certain tumors have utility as diagnostic tools.

The PTO's cited references are not contrary to Applicants' asserted utility

In response to Applicants' arguments, the PTO continues to rely on Haynes, Chen, and Futcher as support for its argument that mRNA levels are not predictive of protein levels. Applicants have discussed at length in previous responses why these references are not relevant to the issue of whether changes in mRNA level for a particular gene leads to changes in protein level. Applicants will not repeat their arguments here.

Previously Submitted Exhibits 2-13 Are Relevant to the PTO's Argument Against Allowance of the Claims

Applicants continue to assert that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1270 polypeptide in lung tumors, it is more likely than not that the PRO1270 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors, and antibodies that bind such proteins, have utility as diagnostic tools.

Applicants previously submitted Exhibits 2-20, comprising numerous references, in support of their argument for the correlation between mRNA levels and protein levels. The PTO fails to address these references in any way. Applicants maintain that the overwhelming evidence they have provided strongly supports Applicants' position.

In addition, Applicants have previously submitted two Polakis Declarations, as well as the Declaration of Dr. Randy Scott, in support of their position that in general, changes in mRNA levels correlate with changes in protein levels. Applicants have provided the opinions of experts in the field that changes in mRNA level for a particular protein in a given tissue generally lead to a corresponding change in the level of the encoded protein. The PTO has failed to address these Declarations in any way.

The case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996)(quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner." *Id.* at 1583. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Part IIB, 66 Fed. Reg. 1098 (2001).

In summary, Applicants have submitted expert Declarations and over 115 references, which support Applicants' asserted utility, either directly or indirectly. This evidence overwhelmingly supports the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions. However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the

evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

The PTO's Position is Inconsistent with the Utility Guidelines and the Courts

In response to Applicants' evidence and arguments, the PTO takes the position that Applicants must present specific evidence directly demonstrating the utility of the claimed polypeptides – specifically, direct evidence of differential expression of PRO1270 polypeptide in tumor and normal tissue. Applicants submit that this requirement is inconsistent with the Utility Guidelines and the courts.

Adopting the PTO's standard for utility would result in a per se rule that a difference in mRNA expression cannot establish a utility for the encoded polypeptide and antibodies thereto. Thus, the PTO chooses to heighten the utility requirement to require specific, direct evidence of utility when there are exceptions to a generally accepted rule that is relied upon for utility. This heightened utility requirement is inconsistent with the Utility Guidelines and the courts. There is no requirement that utility be dispositively proven:

> Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965) ... Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* 2107.02 VII (emphasis in original).

There is no requirement that only direct evidence of utility is sufficient to establish utility. Instead, it is established that indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101. *Nelson v. Bowler*, 626 F.2d 853, 856. Furthermore, there is no requirement that indirect evidence necessarily and always prove actual utility. Instead, there only need be a reasonable correlation between the indirect evidence and the asserted utility. *Id.* at 857, *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051. The indirect evidence need not absolutely prove the asserted utility. All that is required is that the tests be reasonably indicative of the asserted utility. In other words, there need only be a sufficient correlation between the indirect evidence and the utility so as to convince those skilled in the art, to a

reasonable probability, that the novel compound will possess the asserted utility. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564.

In the present case, Applicants submit that their evidence (differential mRNA expression) is reasonably linked to the asserted utility (diagnostic use of the encoded polypeptide). Insofar as it is uncontested that differential mRNA expression is reasonably linked to differential polypeptide expression, Applicants submit that such linkage is sufficient to fulfill the requirements of 35 U.S.C. §101 as provided by the guidance of the Utility Guidelines and the courts.

In conclusion, the PTO's heightened requirement for establishing utility of the presently claimed polypeptides is contrary to the Utility Guidelines and the courts: it is sufficient to present evidence of differential mRNA expression since it is understood in the art that differential mRNA expression is reasonably linked to differential polypeptide expression. As discussed above, even if the PTO has presented evidence that changes in mRNA expression is not always correlated with changes in protein expression, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level typically lead to corresponding changes in protein level. As such, Applicants have established that it is more likely than not that one of skill in the art would believe that because the PRO1270 mRNA is differentially expressed in lung tumors as compared to normal lung tissue, the PRO1270 polypeptide will likewise be differentially expressed in these tumors. Accordingly, when the evidence is applied to the proper standard for utility, it is clear that this differential expression of the PRO1270 polypeptides establishes their utility as diagnostic tools for cancer, particularly lung tumor. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Conclusion

The PTO has asserted that the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels. Applicants have addressed the PTO's supporting references and shown that they are either irrelevant, or taken as a whole, actually support Applicants' assertion that a change in mRNA level leads to a corresponding change in the level of the encoded protein. In addition, Applicants have submitted expert declarations, textbook excerpts, and over 115 scientific publications which support Applicants' asserted utility.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing **some** beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely... A commercially successful product is not required... Nor is it essential that the invention accomplish all its intended functions... or operate under all conditions... partial success being sufficient to demonstrate patentable utility... In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed PRO1270 polypeptides set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO maintains its rejection of Claims 1-5 as lacking enablement. The PTO states that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants respectfully request that to the extent the enablement rejection is based on a lack of utility, the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Jan. 16 2007

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